Pozuelo, J., Nakamura, A. & Mendicuti, F. (1999): Molecular Mechanics Study of the Complexes of β-Cyclodextrin with 4-(dimethylamino)benzonitrile and Benzonitrile. *Journal of inclusion phenomena and molecular recognition in chemistry*, 35 (3), pp.: 467-485.

DOI: 10.1023/A:1008018502072

Molecular Mechanics Study of the Complexes of β-Cyclodextrin with 4-(dimethylamino)benzonitrile and Benzonitrile

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Molecular Mechanics calculations with the Tripos Force Field were employed to study the complexation of 4-(dimethylamino)benzonitrile (DMABN) and/or benzonitrile (BN) with β-cyclodextrin (βCD). The systems studied have 1 : 1 (DMABN : βCD and BN : βCD), 2 : 2 (DMABN : βCD) and 1 : 1 : 2 (DMABN : BN : βCD) stoichiometries. Evidence for the formation of such complexes, binding constants and other thermodynamic parameters were extracted from the analysis of the steady state fluorescence measurements performed in a previous work. The Molecular Mechanics study, based on the energy changes upon guest-host approaching, was performed in vacuo and in the presence of water as a solvent. Results show that the driving forces for 1 : 1 complex-ation are mainly dominated by non-bonded van der Waals host : guest interactions. However, the driving forces for association between 1 : 1 complexes to give 2 : 2 homo- or 1 : 1 : 2 heterodimers are dominated by non-bonded electrostatic interactions. Head-to-head electrostatic interactions between βCDs, which are presumably due to the hydrogen bonding formation between secondary hydroxyl groups of CDs, are responsible for most of the stability of the dimers.

Key words: Cyclodextrins; inclusion complexes; dimers; molecular mechanics calculations

1. Introduction

Cyclodextrins (CDs) are torus-shaped oligosacharides made up of six (αCD), seven (βCD), eight (γCD) or more D-(+)-glucopyranose units joined by α-(1,4) linkages. One of the main characteristics of these cyclic oligosacharides is that they can form inclusion complexes with a variety of guest molecules in aqueous media [1–3]. The complexing properties of CDs are usually attributed to both the size and shape of the inner cavity relative to the guest molecule and the hydrophobicity of the interior relative to the guest and bulk solution media.

Most experimental studies of CDs focus on the binary complexes formed with organic compounds [1–3] where 1 : 1 and/or 1 : 2 guest : host stoichiometries are usually dominant. In this manner, Nakajima [4] and others [5, 6] by measuring

the variation of the I/III pyrene vibronic bands, have reported the sole existence of complexes of pyrene and βCD with 1 : 1 stoichiometry. Kusumoto [7] and Warner [8], however, also reported a 1 : 2 pyrene:βCD complex in addition to the 1 : 1 complex at high concentrations. Supramolecular species of CDs with guests in stoichiometries other than 1 : 1 and 1 : 2 were also observed for binary and ternary complexes containing βCDs. Kano *et al.*, from measurements of pyrene fluorescence quenching by the amines, proposed the formation of ternary 1 : 1 : 1 complexes from aqueous solutions of pyrene + alkylamines + βCD [5, 9]. However, the same author reported how the 1 : 1 : 1 naphthalene + trimethylamine + βCD system enhances exciplex fluorescence [10]. Hamai also studied systems of 1-pyrene sulfonate + aniline + βCD [11] and perylene + *N*, *N*-dimethyl aniline + γCD [12] by fluorescence quenching. Results showed stoichiometries of 1 : 2 : 2 for both complexes. Pyrenes and other polynuclear aromatic compounds also form ternary complexes in the presence of alcohols and CDs [13]. Warner and co-workers [14, 15] have studied the binding of CDs with pyrene in the presence of alcohols by using the variation of the I/III vibronic band ratio of pyrene. In the case of large alcohols, such as cyclopentanol, the data suggest the formation of a predominantly 2 : 1 : 2 pyrene:alcohol:βCD complex. The effect of the presence of alcohols on the inclusion process has also been reported by several of the previously mentioned authors [16–19]. Others have provided evidence for the formation of ternary complexes of CDs, pyrene and surfactants [20–23]. A stoichiometry of 1 : 1 : 2 (guest A : guest B : host) for ternary complexes involving two different guests for two systems, 2-methoxynaphthalene + *o*-phthalonitrile + βCD [24] and 1-cyanonaphthalene + anisole + βCD [25], was also reported by Hamai. Herkstroeter *et al.* [26, 27] and Hamai [28], using UV-vis and fluorescence spectroscopies including lifetime measurements from the first author, found the presence of homodimers with a 2 : 2 stoichiometry by associating two 1 : 1 complexes of 1-pyrenebutyrate and pyrene, respectively, with γCD.

More recently, Nakamura *et al.* [29] reported the aggregation of a 1 : 1 complex of 6-*O*-α-D-glucosyl-β-cyclodextrin (GβCD), a more soluble βCD derivative, and 4-(dimethylamino) benzonitrile (DMABN) into a 2 : 2 homodimer at high concentrations. The 1 : 1 complex of GβCD with DMABN also makes a heterodimer of stoichiometry 1 : 1 : 2 (guest A : guest B : GβCD) with a 1 : 1 inclusion complex of benzonitrile (BN) or anisole. The fluorescence intensity of the guests, which strongly depend on medium polarity, was used to study the stoichiometry and thermodynamic parameters of different complexes in water + acetonitrile (9 : 1 by volume) as a solvent. The equilibrium constants of the DMABN : GβCD (1 : 1) and BN:GβCD (1 : 1) complexes at 25 °C were 158 and 86 (M^{-1}) respectively. The thermodynamic parameters for the complex formation were $\Delta H = -16.6$ kJ mol^{-1} and $\Delta S = -13.6$ J K^{-1} mol^{-1} for DMABN : GβCD (1 : 1) and $\Delta H = +1.1$ kJ mol^{-1} and $\Delta S = +40.7$ J K^{-1} mol^{-1} for BN : GβCD (1 : 1). They also reported equilibrium constants for the DMABN : GβCD (2 : 2) and the DMABN : BN : GβCD (1 : 1 : 2) dimers of 410 and 50 (M^{-1}) respec-

tively, as well as thermodynamic parameters, $\Delta H = -82.3$ kJ mol^{-1} and $\Delta S = -225$ J K^{-1} mol^{-1} for the homodimer and $\Delta H = -66.3$ kJ mol^{-1} and $\Delta S = -190$ J K^{-1} mol^{-1} for the heterodimer.

Molecular Mechanics (MM) [30–44] and Molecular Dynamics (MD) [45–47] have been used successfully to strengthen the understanding of the stability, geometry, driving forces and thermodynamic parameters accompanying inclusion phenomena of small molecules [30–45] and polymers [46, 47] with CDs. Most of the studies performed by Molecular Mechanics (MM) using MM2, MM3, AMBER or Tripos Force Fields have been focused on obtaining the energy changes associated with the transit of the guest molecule through the CD torus coming from large distances for guest:host binary systems of stochiometry 1 : 1.

Here, Molecular Mechanics calculations are used to study 1 : 1, 2 : 2 binary and 1 : 1 : 2 ternary complexes reported by Nakamura *et al.* [29]. Calculations were performed in vacuo and in the presence of water, using the Tripos Force Field [48] and Sybyl 6.3 [49]. The theoretical results, which will give an idea of the geometry and driving forces responsible for 1 : 1 complexation and aggregation, will be discussed in comparison with the experimental thermodynamic parameters associated with such processes.

2. Methods

2.1. COMPUTATIONAL DETAILS

The calculations were performed with Sybyl 6.3 [49] using the Tripos Force Field [48]. The total potential energy of a system was obtained as the sum of six contributions: bond stretching, angle bending, torsion, van der Waals, electrostatic, and out-of-plane (for aromatic conjugated systems). A relative permitivity ϵ as a function of the distance was used for the electrostatics interactions. Instead of the 6-*O*-α-D-glucosyl-β-cyclodextrin of Nakamura's [29] experiments, a βCD was used as the host in all our simulations. An initial check on some of the studied structures demonstrate that the side groups hardly inf uence the results. We have therefore not taken them into account in our calculations, which saved considerable computer time. Host (βCD) and guest (DMABN, BN) geometries and charges, obtained by MOPAC [50] are collected in Tables I and II. The labelling of the atoms for D(+)-glucopyranose units, DMABN and BN is depicted in Figure 1. Extended non-bonded cut-off distances were set at 8 Å for van der Waals and electrostatics interactions. Minimization of the potential energy of the system was performed by the simplex algorithm [51,52] and the conjugate gradient was used as a termination method [52]. The termination gradients were 0.2 and 3.0 for the calculations performed in vacuo and in water, respectively. Charges and geometry for water molecules were also obtained by MOPAC [50]. H and O atoms have partial charges of +0.192 and −0.394 ecu respectively, O-H bonds have lengths of 0.95 Å and H—O—H atoms form an angle of 104.5°. Solvation was achieved by using the Molecular Silverware algorithm (MS) [53]. PBC conditions were employed using

Table I. Bond lengths, bond angles and partial charges in the D-glucopyranose units.

Bond	Length (Å)	Bonds	Angle (deg)	Atom[a]	Charge (ecu)
C(1)—C(2)	1.547	O(5)—C(1)—C(2)	109.9	C(1)	0.327
C(2)—C(3)	1.544	C(1)—C(2)—C(3)	109.1	C(2)	0.096
C(3)—C(4)	1.554	C(2)—C(3)—C(4)	109.7	C(3)	0.098
C(4)—C(5)	1.558	C(3)—C(4)—C(5)	108.1	C(4)	0.121
C(5)—O(5)	1.444	C(4)—C(5)—O(5)	110.1	C(5)	0.144
C(1)—O(5)	1.437	C(5)—O(5)—C(1)	114.3	C(6)	0.167
C(2)—O(2)	1.440	C(1)—C(2)—O(2)	109.2	O(2)	−0.315
C(3)—O(3)	1.439	O(2)—C(2)—C(3)	110.6	O(3)	−0.330
C(4)—O(4)	1.446	C(2)—C(3)—O(2)	108.0	O(4)	−0.359
C(5)—C(6)	1.551	O(3)—C(3)—C(4)	112.5	O(5)	−0.352
C(6)—O(6)	1.440	C(3)—C(4)—O(4)	105.5	O(6)	−0.317
C(1)—O(4′)	1.442	O(4)—C(4)—C(5)	115.3		
		C(4)—C(5)—C(6)	113.7		
		C(6)—C(5)—O(5)	104.5		
		C(5)—C(6)—O(6)	108.6		
		O(4′)—C(1)—C(2)	109.2		
		C(4)—O(4)—C(1′)	115.6		
		O(4′)—C(1)—O(5)	111.5		

[a] Charges for hydrogen atoms (not tabulated) produce a neutral molecule.

a cubic box with sides of 31.87 Å for any of the 1 : 1, 2 : 2 or 1 : 1 : 2 complexes studied.

2.2. COMPLEXATION AND ASSOCIATION INTO DIMERS

As in other works [43, 44, 46, 47], the initial structure of the βCD was in the non-distorted form. Following the usual nomenclature, the torsional angles ϕ and ψ were fixed at 0° and −3°, respectively, all glycosidic oxygen atoms O(4′) were placed in the same plane and the bond angles C(1)—O(4′)—C(4) were at 121.7°. The $C^{ar}(1)$—N(2) initial torsional angle value for the DMABN guest can be found in Table II.

For the inclusion process of 1 : 1 complexes, the βCD molecule was fixed so that the center of mass of its seven glycosidic oxygen atoms (denoted by *O* in Figure 2) was located at the origin of a Cartesian coordinate system. The *y* axis of this coordinate system refers to the seven-fold rotation CD axis and it passes through the centroids, depicted in Figure 2, defined by the primary hydroxyl and secondary hydroxyl groups respectively. The *z* axis passes through one of seven

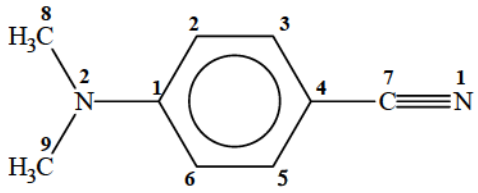
Table II. Bond lengths, angles and partial charges in DMABN and BN[a].

Bond	Length (Å)	Bonds	Angle (deg)	Atom[b]	Charge (ecu)
C(1)—C(2)	1.410 (1.395)	C(1)—C(2)—C(3)	120.74 (120.19)	C(1)	0.030 (−0.108)
C(2)—C(3)	1.390 (1.394)	C(2)—C(3)—C(4)	119.98 (119.77)	C(2)	−0.162 (−0.133)
C(3)—C(4)	1.402 (1.402)	C(3)—C(4)—C(5)	119.77 (119.97)	C(3)	−0.085 (−0.092)
C(4)—C(5)	1.401 (1.402)	C(4)—C(5)—C(6)	120.34 (119.85)	C(4)	−0.020 (−0.011)
C(5)—C(6)	1.392 (1.393)	C(5)—C(6)—C(1)	120.35 (120.13)	C(5)	−0.092 (−0.092)
C(6)—C(1)	1.409 (1.396)	C(6)—C(1)—C(2)	118.81 (120.10)	C(6)	−0.114 (−0.133)
C(4)—C(7)	1.421 (1.421)	C(3)—C(4)—C(7)	120.08 (120.01)	C(7)	−0.095 (−0.097)
C(7)—N(1)	1.164 (1.164)	C(2)—C(1)—N(2)	122.75	C(8)	−0.118
C(1)—N(2)	1.437	C(1)—N(2)—C(8)	112.87	C(9)	−0.118
N(2)—C(8)	1.448	C(1)—N(2)—C(9)	112.88	N(1)	−0.039 (−0.037)
N(2)—C(9)	1.448	C(2)—C(1)—N(2)—C(8)	65.0	N(2)	−0.233
		C(6)—C(1)—N(2)—C(9)	115.0		

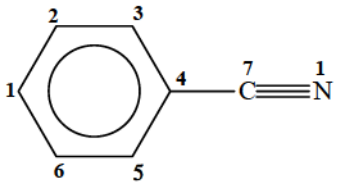
[a] Values for BN are in parentheses.
[b] Charges for hydrogen atoms (not tabulated) produce a neutral molecule.

glycosidic oxygens and the x-z plane is def ned by these oxygen atoms. The host-guest distance was taken as the OO' distance along the y coordinate, where O' represents the centroid of the guest molecule benzene ring. The inclusion angle θ was measured between y-z and the guest molecule aromatic ring planes. The calculations reported here were performed where the amino and benzene group sides for DMABN and BN, respectively, approach the host, as depicted at the top of Figure 2. An initial calculation of the energy change upon the host-guest approach revealed that this orientation is prefered over the one where the guest molecules penetrate by the cyano group side. For the complexation process, the guest molecule was moved incrementally in small steps of 0.5 Å along the y axis from 16 Å to −2 Å.

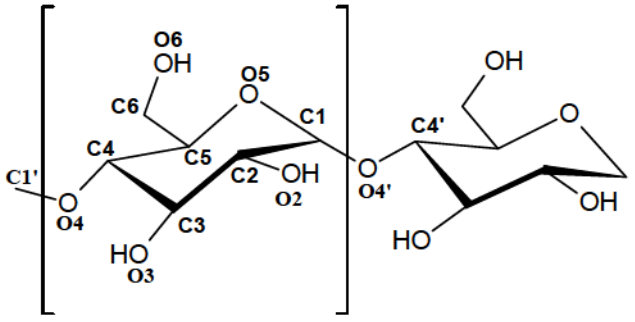
The association or aggregation process of two 1 : 1 guest : host complexes, which is also depicted at the bottom of Figure 2, was carried out in a similar manner. Initially, one of the structures of minimum binding energy of each of the 1 : 1 complexes was placed with the center of the mass of glycosidic oxygen atoms O of the βCD at the origin of the coordinate system def ned in the previous paragraph, and the center of mass of the glycosidic oxygen atoms O' of the βCD of the other one at 18 Å on the positive side of the y axis. On the basis of the studies performed on polyrotaxanes where the most favourable interaction between CDs occurs when they are head-to-head oriented [46, 47], the approach between 1 : 1 complexes was carried out as depicted in Figure 2. Now OO' def nes the distance between 1 : 1 complexes, which is changed from 18 Å to 6 Å at 0.5 Å intervals during the association process. The association angle θ is measured by the dihedral



DMABN



BN



Glucopyranose Unit

Figure 1. Labelling of the DMABN and BN guests and a pair of glucopyranose units of the βCD host.

angle O(4)-O − O'-O(4′) where O(4) and O(4′) are glycosidic oxygens (on the z and z' axis) of the CDs of each 1 : 1 complex. Initially, this angle was placed at 0° and it hardly changes upon association. No constraints were applied to either the host : guest distance ($O\,O'$) or the inclusion (and association) angle θ.

The binding energy, E_{binding}, which is associated to the enthalpy change between the guest and the CD for a 1 : 1 complex was obtained as the difference between the potential energy of the guest : CD system and the sum of the potential energies of isolated guests and CDs in the same conformation as,

$$E_{\text{binding}} = E_{\text{CD : guest}} - (E_{\text{isolated CD}} + E_{\text{isolated guest}}). \quad (1)$$

E_{binding} in the presence of water was obtained by removing the water molecules from the box before applying Equation (1). In a similar manner, non-bonded A-B interactions (or any of the contributions) between two components (A) and (B) of a system (A + B) can be obtained as the difference of the total potential energy

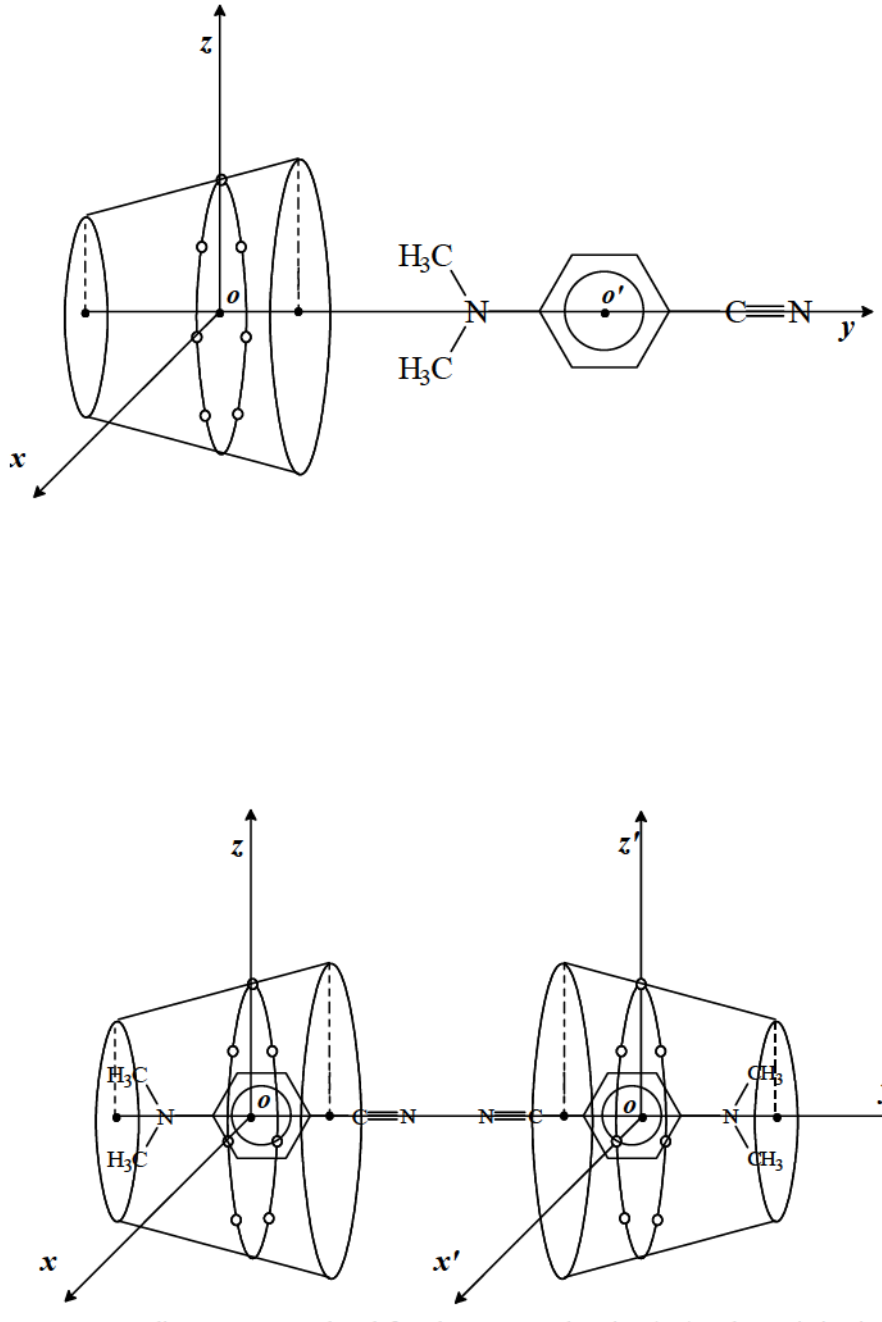


Figure 2. Coordinate system used to def ne the 1 : 1 complexation (top) and association into dimers (bottom) and schemes for both processes.

of the whole system (A + B) and the sum of potential energies of isolated A and B in the same conformation. The strain energy of CDs was obtained as the sum of torsional, stretching and bending energies. A measure of the inf uence of the solvent on complexation was obtained as the non-bonded energy interaction of water molecules and the complex. All energies and contributions were obtained as a function of the OO' distance.

A hydrogen bond is assumed when hydrogen, bonded to a donor, and the acceptor approach a distance in the range of 0.8–2.8 Å and the angle formed by the donor, the hydrogen and the acceptor is $>120°$.

3. Results and Discussion

3.1. COMPLEXATION IN VACUO

Initially the path was determined for the most favorable approaches of DMABN and BN to the βCD. For this purpose, E_{binding} for all optimized structures was obtained by scanning the inclusion angle θ from 0 to 55° at 5° intervals and the OO' distance along the y coordinate from 16 to -2 Å at 1 Å intervals. The trajectory of the lowest energy for the approach was selected from three-dimensional plots. E_{binding} minima are placed at around the origin of the coordinate system and θ = 0° and 51°, of which the more negative E_{binding} corresponds to θ = 51° for both DMABN : βCD and BN : βCD (1 : 1) complexes. Nevertheless, the inf uence of θ on E_{binding} is not very important. In the remainder of the study the inclusion angle was initially f xed at 51° and the coordinate y was changed from 16 to -2 Å for 1 : 1 complexation.

Figure 3 depicts E_{binding} for the complexes DMABN : βCD and BN : βCD for the optimized structures obtained by scanning y in the range indicated at 0.5 Å intervals for the trajectories of θ = 51° before optimization. E_{binding} decreases monotonically when the guest approaches the CD host. The minima E_{binding} are reached at approximately $y = +1$ and -1 Å and the inclusion angle hardly changes from the initial value. The structure of complexes for these minima indicates that BN totally penetrates into the βCD cavity and a slight portion of DMABN is exposed to the outside. The absence of gaps in the curves depicted in Figure 3 (a and b) denotes that repulsive interactions, which are usually strong for the inclusion of large size guest molecules, are not important. According to Figure 3, changes of E_{binding} upon complexation, whose values are included in Table III, are more negative for the DMABN complexation than for the BN complexation. Molecular Mechanics calculations provide a potential energy and any change in energies upon complexation corresponds to an enthalpy difference for the process. They do not provide entropy changes. E_{binding} corresponds to an enthalpy difference between the free and complexed states. Our simple MM calculations in vacuo only reveal that DMABN : βCD complex formation should be relatively more favoured enthalpically than the formation of BN : βCD. Experimental changes of enthalpy

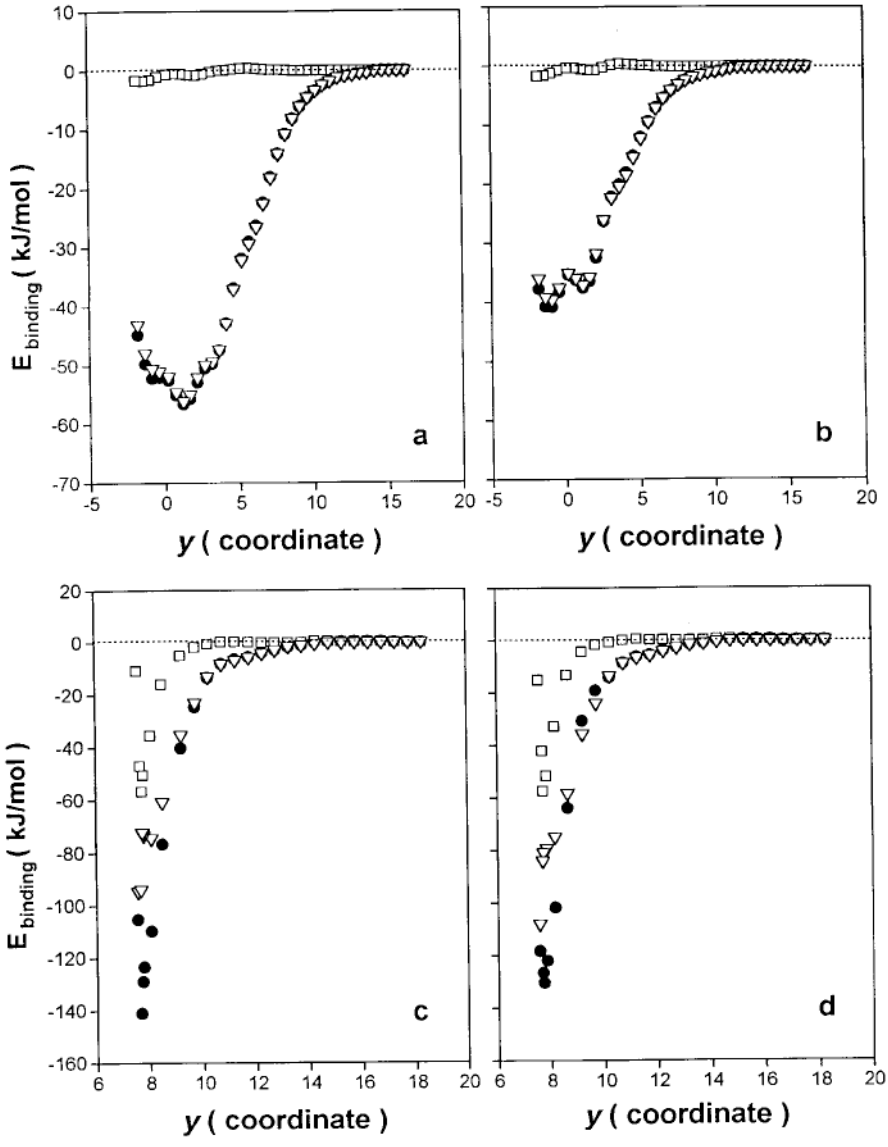


Figure 3. $E_{binding}$ (●), van der Waals (▽) and electrostatic (□) contributions as a function of the y coordinate (Å) in vacuo for (a) DMABN : βCD (1 : 1), (b) DMABN : βCD (1 : 1), (b) BN : βCD (1 : 1), (c) DMABN : βCD(2 : 2) and (d) DMABN : BN : βCD (1 : 1 : 2).

reported by Nakamura *et al.* [29] were −16.6 and +1.1 kJ/mol for 1 : 1 complexes of GβCD with DMABN and BN respectively, in water-acetonitrile. In fact, formation of a 1 : 1 complex is enthalpy driven for DMABN and entropy driven for BN.

Table III. $E_{binding}$ and selected components (kJ/mol), electrostatics and van der Waals, at the minimum binding energy for the complexes in vacuo and in water.

	$E_{binding}$ (kJ/mol)					
	Vacuo			Solvent		
Complex (stoichiometry)	Total	Elec.	vdW	Total	Elec.	vdW
DMABN : βCD (1 : 1)	−56.4	−0.4	−56.0	−56.0	−0.4	−55.6
BN : βCD (1 : 1)	−41.0	−0.4	−40.6	−35.9	−0.8	−35.1
DMABN : βCD (2 : 2)	−140.9	−46.8	−94.1	−102.0	−61.5	−40.5
DMABN : BN : βCD (1 : 1 : 2)	−138.4	−57.3	−81.1	−88.6	−56.4	−32.2

Figure 3, a and b, also depicts the van der Waals and electrostatics contributions to $E_{binding}$ during the 1 : 1 complexation processes. The most important contribution to $E_{binding}$ is due to van der Waals guest-host interactions. Electrostatics represents less than 1% of the binding energy. Table III collects these contributions.

As for the 1 : 1 complex formation, the association process to give DMABN : βCD (2 : 2) and DMABN : BN : βCD (1 : 1 : 2) complexes, depicted in Figure 3,c and d, is accompanied by a decrease in binding energy as the distance decreases up to approximately 7.8 Å. The electrostatics contributions, however, are much more important. They represent approximately one third of the value of $E_{binding}$ for the structure of the minimum binding energy. Table III collects $E_{binding}$ and the van der Waals and electrostatics contributions for the structure of minimum binding energy obtained by scanning y from 18 to 6 Å at 0.5 Å intervals. According to Table III, $E_{binding}$ is considerably more negative for the 1 : 1 association into dimers than for the formation of 1 : 1 complexes. This fact agrees with the large negative enthalpies for the association into homo- and heterodimers as compared with the formation of 1 : 1 complexes reported by Nakamura *et al.* [29] for similar compounds. The homodimer also shows a slightly more negative $E_{binding}$ than the heterodimer.

3.2. COMPLEXATION IN WATER

Solvation was performed by using the MS algorithm [53]. This simple method consists in adding solvent molecules in such manner that the solvent and solute van der Waals surfaces do not overlap. The complexation process was simulated by method I of Madrid *et al.* [43, 44] used to explain the geometry of the 1 : 1 complexes of a derivative of naphthalene with α-, β- and γCDs which were substantially different from the ones in vacuo. Brief y, each structure generated by changing the host-guest distance was solvated and then the potential energy was minimized.

Figure 4a and b, depicts the variation of $E_{binding}$ for 1 : 1 DMABN : βCD and BN : βCD complexes obtained by scanning y from 16 to −2 Å at 0.5Å intervals for

the trajectories of θ initially located at 51°. Minimum values of binding energies are reached at approximately $y = 1$ Å for both complexes, which means that both guests penetrate almost totally into the cavity. Figure 5 depicts structures of minimum binding energies for DMABN : βCD (1 : 1) and BN : βCD (1 : 1). Most of the guest molecule is shielded by the CD host and only a small portion of the cyano group side is exposed to the solvent. There are no differences in the structures to explain the signs of entropy changes associated with both complexation processes. Table III also collects values of E_{binding} energies and contributions from the analysis of the results in the presence of water, which are −56.0 and −35.9 kJ/mol respectively. As in vacuo DMABN : βCD complexation is accompanied by a more negative binding energy than the BN : βCD one, the most important contributions are also due to van der Waals interactions.

Figure 4,c and d, also depicts the variation of E_{binding} and van der Waals and electrostatics contributions for the association of 1 : 1 complexes into homo- and heterodimers. Minimum E_{binding} structures have approximately $y = 7.8$ Å and the binding energies are −102.0 and −88.6 kJ/mol for homo- and heterodimer. In the presence of water, electrostatics represents the largest contribution. Approximately 61% of this E_{binding} is due to the electrostatics contribution for DMABN : βCD (2 : 2) and 64% for DMABN : BN : βCD (1 : 1 : 2). Figure 6 depicts structures of homo- and heterodimer complexes for the minimum binding energies. In the homo- and heterodimers guest molecules are perfectly shielded against exposure to the solvent, even better than they were in the 1 : 1 complexes. This different exposure during association, if it were really considerable, should signify an entropy increase. The large negative ΔS for association reported by Nakamura *et al.* [29] should only be explained as due to the loss of degrees of freedom during the joining of two 1 : 1 complexes into a dimer.

Table IV collects data of non-bonded binding energies between different components of the complexes, as well as their van der Waals and electrostatics contributions for homo- and heterodimers in the presence of water. Non-bonded binding interaction values between the CD and guest molecule of each 1 : 1 complex denotes that association into 2 : 2 or 1 : 1 : 2 homo- or heterodimer is accompanied by a slight decrease of this negative contribution. However, this decrease is compensated by a strong attractive non-bonded head-to-head interaction between CD host molecules. Data collected in lines 10–12 of Table IV indicate that the main contribution to CD-CD interaction is electrostatics. This attractive interaction was similar to the one observed between CDs in polyrotaxanes [46, 47]. However, as depicted in lines 13–15 of Table IV, intermolecular interactions due to guest molecules hardly inf uence the stabilization of the system. The stabilization of dimers due to the electrostatic interaction between CDs must arise from the presence of intermolecular hydrogen bonds (HB) between CDs. CDs in the complexes, particularly for dimers, are not signif cantly distorted. This fact favours the presence of intra- and intermolecular HBs. For the structures of minimum binding energy depicted in Figure 6, according to the criteria of HB formation, a total of

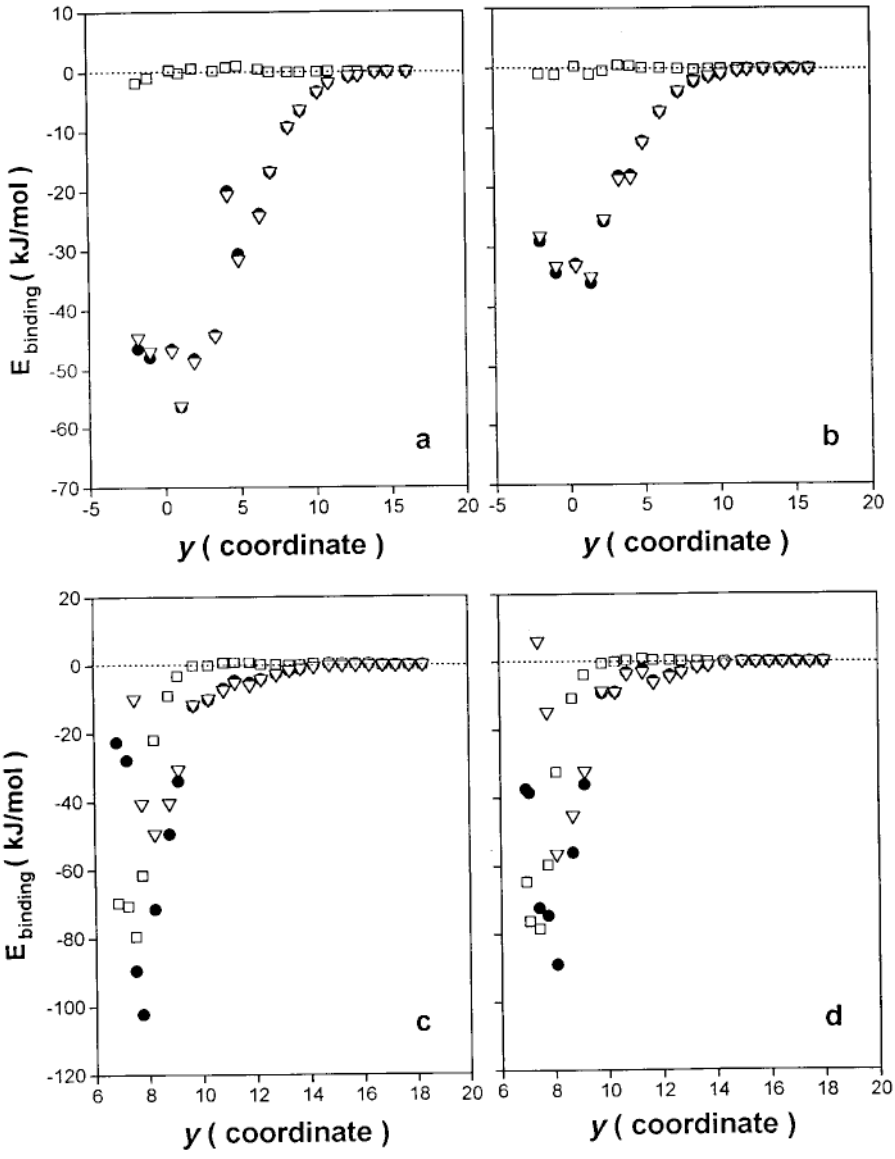


Figure 4. $E_{binding}$ (●), van der Waals (▽) and electrostatic (□) contributions as a function of the y coordinate (Å) in water for (a) DMABN : βCD (1 : 1), (b) BN : βCD (1 : 1), (c) DMABN : βCD(2 : 2) and (d) DMABN : BN : βCD (1 : 1 : 2). complexes.

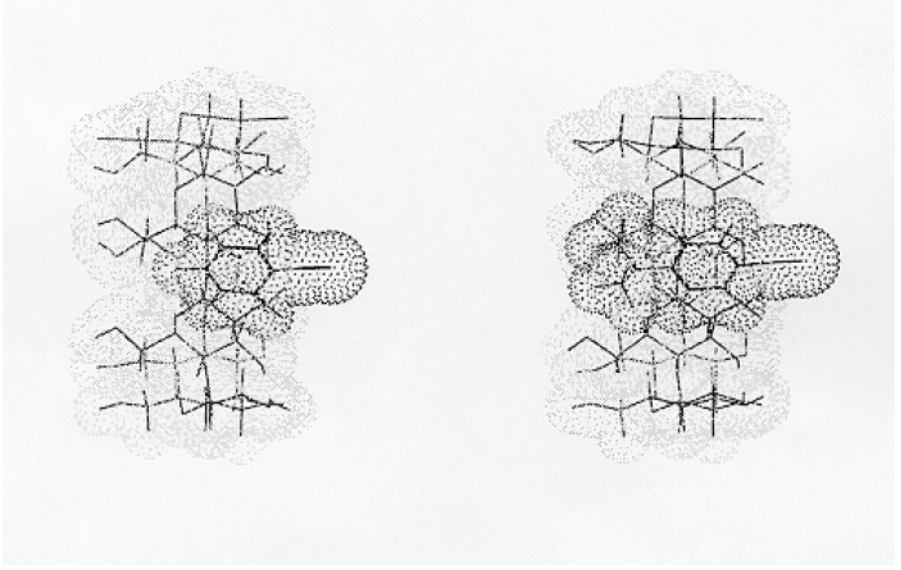


Figure 5. van der Waals surfaces for (right) DMABN:βCD (1 : 1) and (left) BN:βCD (1 : 1). Most of the guest molecules are shielded by the CD host.

13 and 14 intermolecular HBs can be formed between CDs whose presence must contribute to the large negative ΔH value for the association. Additional calculations of the non-bonded electrostatic interactions between donor and acceptor pairs reveal that this contribution is very important in the stabilization of the system.

The total potential energy of the βCD, as well as several contributions, are depicted in Figure 7 for 1 : 1 complexation and for association of the 1 : 1 complex into a 1 : 1 : 2 complex. In both cases, torsion, bending and stretching terms contribute most to the total βCD energy. 1 : 1 complexation and association processes are both accompanied by almost no increases in the potential energy of the CD or any of its components. Neither the 1 : 1 complexation nor the association into dimers are carried out with any apparent distortion or relaxation of the βCD macrorings. The CD cavity is long enough to include any DMABN or BN guest molecule. The approach of 1 : 1 complexes up to approximately the optimum distance of 7.8 Å also takes place without any change of total potential energy of the CD or any of its components.

The presence of water is quantif ed by the term $E_{\text{complex}-\text{water}}$ which represents the complex-water energy interaction. Figure 8 depicts this energy as a function of the y coordinate. Both 1 : 1 complexation and association into dimers are accompanied by an increase of this energy which contributes signif cantly to destabilizing the system. The hydration energy serves as a source of destabilization for the complexes. This fact was observed previously for other 1 : 1 complexes [43, 44].

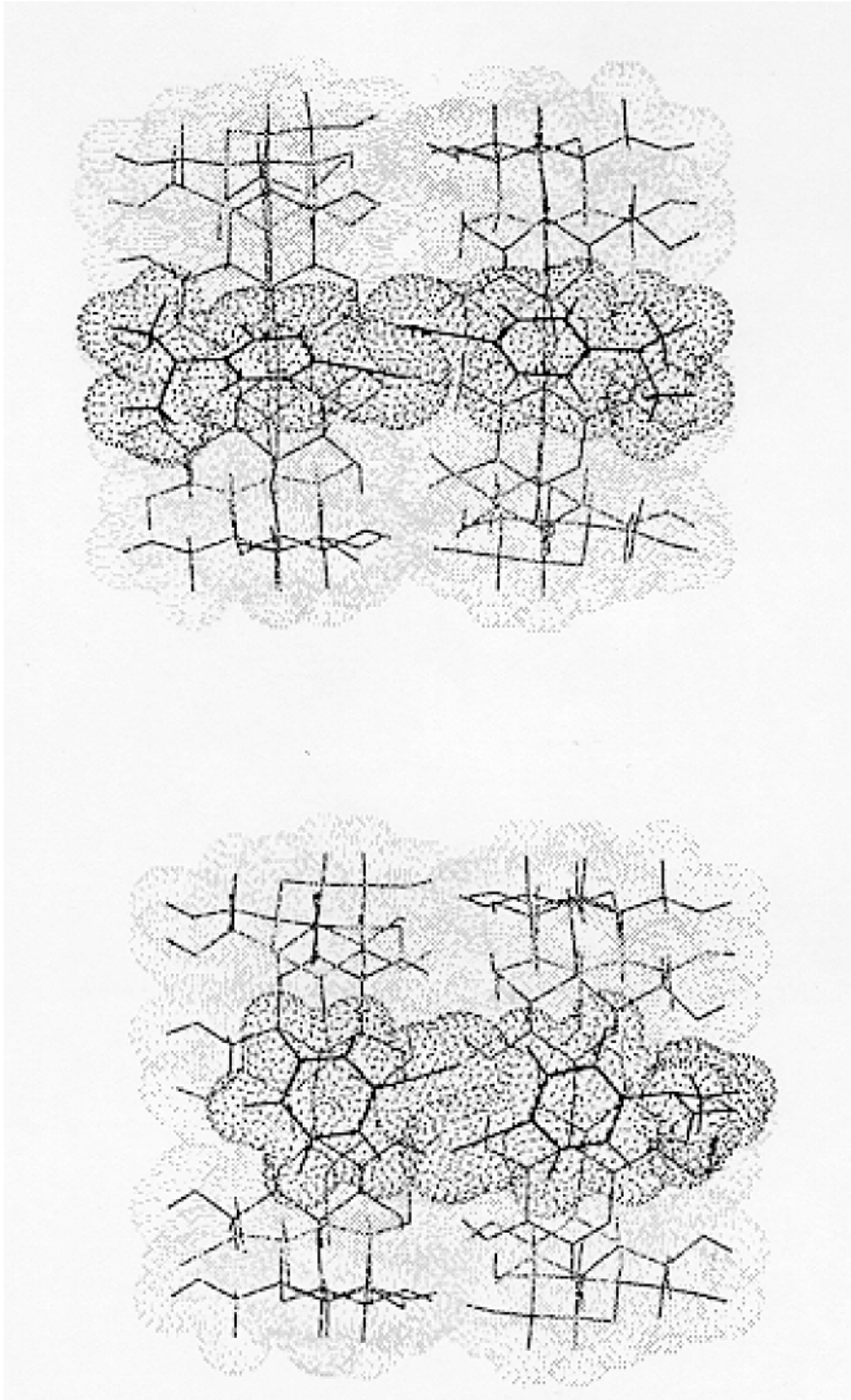


Figure 6. van der Waals surfaces for (top) DMABN : βCD(2 : 2) homodimer and (buttom) DMABN:BN:βCD (1 : 1 : 2) heterodimer. CDs perfectly shield the guest molecules from the solvent.

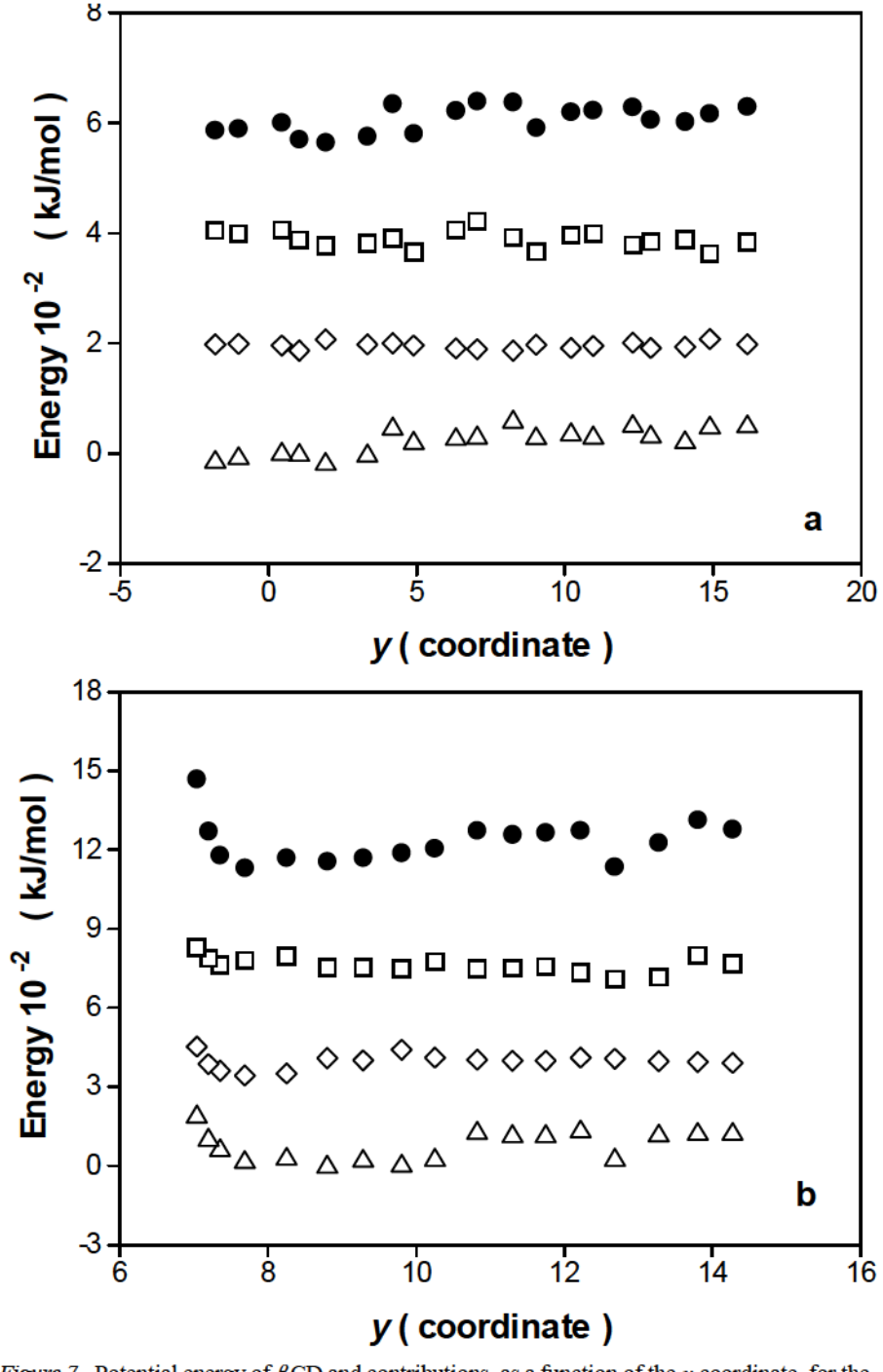


Figure 7. Potential energy of βCD and contributions, as a function of the y coordinate, for the (top) DMABN : βCD (1 : 1) and (bottom) DMABN : BN : βCD (1 : 1 : 2) heterodimer in water. The energies are (●) total, (△) van der Waals and (◇) electrostatic, and (□) sum of stretching, bending, and torsion.

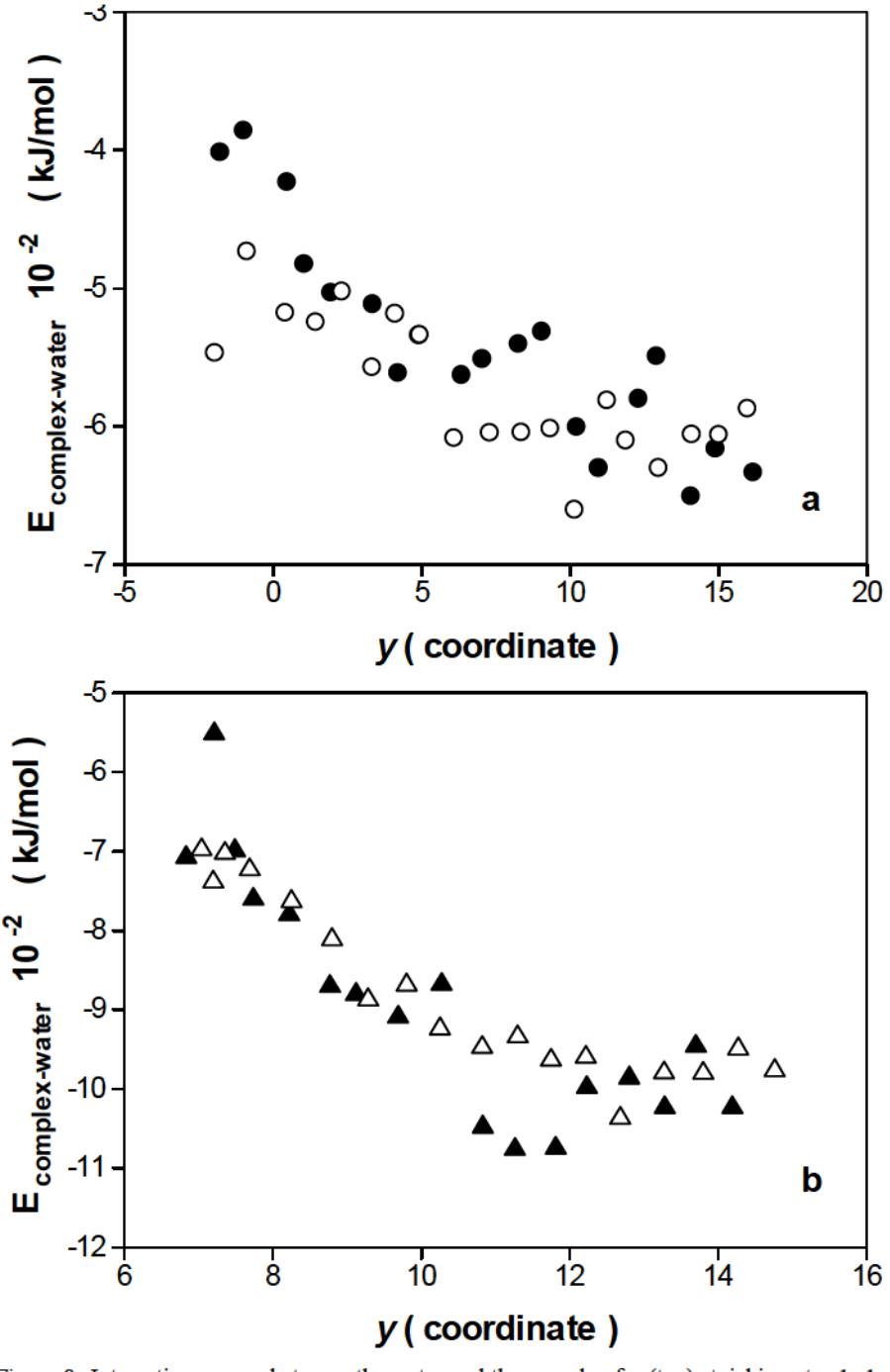


Figure 8. Interaction energy between the water and the complex for (top) stoichiometry 1 : 1 (●) DMABN : βCD and (○) BN : βCD complexes and (bottom) (s) DMABN : βCD (2 : 2) and (Δ) DMABN : BN : βCD (1 : 1 : 2) dimers.

Table IV. Non-bonded binding interaction energies and selected contributions between different components for homo- and heterodimers for the structures of minimum binding energies. Nomenclature in parentheses indicates binding interaction between 1 : 1 complexes (CD_1B_1-CD_2B_2), between a CD and its guest (CD_1-B_1) and the other CD and its guest (CD_2-B_2), between both CDs (CD_1-CD_2)and between both guest molecules (B_1:B_2).

Non-bonded binding energies (kJ/mol)	βCD : DMABN (2 : 2)	βCD : DMABN : BN (1 : 1 : 2)
$E_{binding}$ (CD_1B_1-CD_2B_2)	−102.0	−88.6
van der Waals part	−40.4	−32.2
Electrostatics part	−61.6	−56.4
$E_{binding}$ (CD_1-B_1)	−44.3	−53.5
van der Waals part	−44.7	−53.5
Electrostatics part	0.4	0.0
$E_{binding}$ (CD_2-B_2)	−55.2	−28.4
van der Waals part	-55.2	-28.4
Electrostatics part	0.0	0.0
$E_{binding}$ (CD_1-CD_2)	−92.0	−86.5
van der Waals part	−29.3	−21.7
Electrostatics part	−62.7	−64.8
$E_{binding}$ (B_1-B_2)	0.4	−0.4
van der Waals part	0.0	−0.4
Electrostatics part	0.4	0.0

4. Conclusions

Molecular Mechanics calculations applied to the study of the (1 : 1) complexation of DMABN : βCD and BN : βCD and of the association process into a (2 : 2) DMABN : βCD homodimer and a (1 : 1 : 2) DMABN : BN : βCD heterodimer, are capable of predicting the experimental evidence [29] of the formation of such complexes. The non-bonded van der Waals interactions seem mainly responsible for the formation of 1 : 1 complexes, whereas, association of 1 : 1 complexes into dimers is mainly due to non-bonded electrostatic interactions between CDs. Complexation or association does not seem to be accompanied by a noticeable increase in the strain or release of the CD macroring. As with other complexes, the water-complex interaction seems to stabilize the uncomplexed form. Relative binding energies for 1 : 1 complexes and dimers seem to explain the relative changes of enthalpy upon formation. Dimers have considerably more negative binding energies than 1 : 1 complexes. In the structures of minimum binding energies for dimers the DMABN or BN guests are suff ciently shielded from the solvent molecules to ensure that the

strong loss in entropy during association should arise from the loss in the degrees of freedom of the associated dimer.

Acknowledgements

This research was supported by CICYT grant PB94-0364. We wish to express our thanks to M.L. Heijnen for assistance with the preparation of the manuscript.

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